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Dated 21 June 2004

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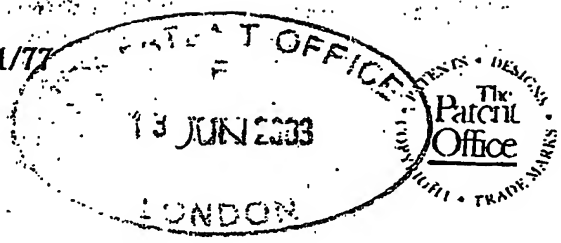

16JUN03 E815022-1 D02639
P01/7700 0.00-0313772.6

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

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1. Your reference — 13 JUN 2003

2. Patent application number *(The Patent Office will fill in this part)* — T1633PV — 0313772.6

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

Patents ADP number *(if you know it)*

00597799001

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

4. Title of the invention

Therapeutic treatment

Name of your agent *(if you have one)*

Dr. G. M. Buchan

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Merck & Co., Inc.
European Patent Department
Terlings Park
Eastwick Road
Harlow
Essex CM20 2QR

Patents ADP number *(if you know it)*

44879001

If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

any applicant named in part 3 is not an inventor, or
there is an inventor who is not named as an applicant, or
any named applicant is a corporate body.
see note (d))

Yes

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	0
Description	26
Claim *(s)*	0
Abstract	0
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Priority documents	–
Translations of priority documents	–
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	–
Request for preliminary examination and search *(Patents Form 9/77)*	–
Request for substantive examination *(Patents Form 10/77)*	–
Any other documents *(please specify)*	–

11. I/We request the grant of a patent on the basis of this application.

Signature G M Buchan Date 13 June 2003

Dr. G. M. Buchan

12. Name and daytime telephone number of person to contact in the United Kingdom

Dr. G. M. Buchan 01270 440568

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THERAPEUTIC TREATMENT

This invention relates to the use of methods and materials for therapeutic treatment of the human body. In particular, it provides methods of treating diseases associated with the deposition of β-amyloid in the brain, such as Alzheimer's disease, or of preventing or delaying the onset of dementia associated with such diseases.

Alzheimer's disease (AD) is the most prevalent form of dementia. Its diagnosis is described in the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., published by the American Psychiatric Association (DSM-IV). It is a neurodegenerative disorder, clinically characterized by progressive loss of memory and general cognitive function, and pathologically characterized by the deposition of extracellular proteinaceous plaques in the cortical and associative brain regions of sufferers. These plaques mainly comprise fibrillar aggregates of β-amyloid peptide (Aβ). Aβ is formed from amyloid precursor protein (APP) via separate intracellular proteolytic events involving the enzymes β-secretase and γ-secretase. Variability in the site of the proteolysis mediated by γ-secretase results in Aβ of varying chain length, e.g. Aβ 1-38, 1-40 and 1-42. After secretion into the extracellular medium, the initially-soluble Aβ forms aggregates which ultimately result in the insoluble deposits and dense neuritic plaques which are the pathological characteristics of AD.

Other dementing conditions associated with deposition of Aβ in the brain include cerebral amyloid angiopathy, multi-infarct dementia, dementia pugilistica and Down syndrome.

Various interventions in the plaque-forming process have been proposed as therapeutic treatments for AD (see, for example, Hardy and Selkoe, *Science*, **297** (2002), 353-6). One such method of treatment that has been proposed is that of blocking or attenuating the production of Aβ, for example by inhibition of β- or γ-secretase. Compounds which inhibit γ-secretase are disclosed in WO 01/53255, WO 01/66564, WO 01/70677, WO

01/90084, WO 01/77144, WO 02/30912, WO 02/36555, WO 02/081435, WO 02/081433, WO 03/018543, WO 03/013506, WO 03/013527 and WO 03/014075. Compounds which inhibit β-secretase are disclosed in WO 03/037325, WO 03/030886, WO 03/006013, WO 03/006021, WO 03/006423, WO 03/006453, WO 02/002122, WO 01/70672, WO 02/02505, WO 02/02506, WO 02/02512, WO 02/02520, WO 02/098849 and WO 02/100820. Other compounds which inhibit the formation or release of Aβ include those disclosed in WO 98/28268, WO 02/47671, WO 99/67221, WO 01/34639, WO 01/34571, WO 00/07995, WO 00/38618, WO 01/92235, WO 01/77086, WO 01/74784, WO 01/74796, WO 01/74783, WO 01/60826, WO 01/19797, WO 01/27108, WO 01/27091, WO 00/50391, WO 02/057252, US 2002/0025955 and US2002/0022621.

It has also been reported that inhibition of glycogen synthase kinase-3 (GSK-3), in particular inhibition of GSK-3α, can block the production of Aβ (see Phiel et al, *Nature*, **423** (2003), 435-9).

Another such method of treatment that has been proposed is that of modulation of the action of γ-secretase so as to selectively attenuate the production of Aβ (1-42). This results in preferential secretion of the shorter chain isoforms of Aβ, which are believed to have a reduced propensity for self-aggregation and plaque formation, and hence are more easily cleared from the brain, and/or are less neurotoxic. Compounds showing this effect include certain non-steroidal antiinflammatory drugs (NSAIDs) and their analogues (see WO 01/78721 and US 2002/0128319). Compounds which modulate the activity of PPARα and/or PPARδ are also reported to have the effect of lowering Aβ 1-42 (WO 02/100836). NSAID derivatives capable of releasing nitric oxide have been reported to show improved anti-neuroinflammatory effects and/or to reduce intracerebral Aβ deposition in animal models (WO 02/092072; Jantzen et al, *J. Neuroscience*, **22** (2002), 226-54).

Another such method of treatment that has been proposed is that of administering a compound which blocks the aggregation of Aβ.

Compounds having this property include chelating agents such as clioquinol (Gouras and Beal, *Neuron*, **30** (2001), 641-2) and the compounds disclosed in WO 99/16741, in particular that known as DP-109 (Kalendarev et al, *J. Pharm. Biomed. Anal.*, **24** (2001), 967-75). Other inhibitors of Aβ aggregation include the compounds disclosed in WO 96/28471, WO 98/08868 and WO 00/052048, including the compound known as Apan™ (Praecis), WO 00/064420, WO 03/017994, WO 99/59571 and the compound known as Alzhemed™ (Neurochem), WO 00/149281 and the compositions known as PTI-777 and PTI-00703 (ProteoTech), WO 96/39834, WO 01/83425, WO 01/55093, WO 00/76988, WO 00/76987, WO 00/76969, WO 00/76489, WO 97/26919, WO 97/16194, and WO 97/16191.

Another such method of treatment that has been proposed is that of administering an antibody which selectively binds to Aβ. Such antibodies may be brain-penetrant and capable of binding to insoluble Aβ, as described in WO 99/60024 and WO 00/72880 for example. Alternatively, such antibodies may be capable of sequestering soluble Aβ from biological fluids, without necessarily being brain-penetrant. It is believed that in these circumstances the removal of unbound Aβ from the serum increases the relevant concentration gradient between brain and serum, causing an efflux of Aβ from the brain to the serum. This approach is described in WO 03/016466, WO 03/016467, WO 03/015691 and WO 01/62801.

Growth hormone has been proposed for use in treatment of AD. Thus, US 4,902,680 advocates the administration of growth hormone to patients in the advanced stages of AD, while WO 00/13650 discloses that increased levels of growth hormone in the brain provide a neuroprotective effect, and in particular can rescue neurons that would otherwise die as a result of an insult such as that associated with a neurodegenerative disease such as AD. The injection of growth hormone into the brain is contemplated.

Growth hormone secretagogues (GHSs) are compounds which, when administered to an animal (such as a human), stimulate or increase the

release of endogenous growth hormone in the animal. Their mode of action and clinical utilities are reviewed by Ankersen et al, *Drug Discovery Today*, **4** (1999), 497-506; Casanueva and Dieguez, *TEM*, **10** (1999), 30-8; Smith et al, *ibid.*, **10** (1999), 128-35; Betancourt and Smith, *J. Anti-Aging Med.*, **5** (2002), 63-72; and Ghigo et al, *ibid.*, **5** (2002), 345-56, but there is no mention of treating AD or any other neurodegenerative condition. Patents and patent applications disclosing compounds which are GHSs include US 5,767,124, US 5,536,716, WO 94/13696, EP 0615977B, US 5,578,593; WO 01/04119, WO 98/25897, WO 98/10653, WO 97/36873, WO 97/34604, WO 97/15574, WO 97/11697, WO 96/32943, WO 96/13265, WO 96/02530, WO 95/34311, WO 95/14666, WO 95/13069, WO 94/19367, WO 94/05634 and WO 92/16524 (all assigned to Merck & Co., Inc.); EP 1002802A, EP 0995748A, WO 98/58948, WO 98/58947 and WO 97/24369 (all assigned to Pfizer Inc.); WO 01/34593, WO 00/26252, WO 00/01726, WO 99/64456, WO 99/58501, WO 99/36431, WO 98/58950, WO 98/08492, WO 98/03473, WO 97/40071, WO 97/40023, WO 97/23508, WO 97/00894, WO 96/24587, WO 96/24580, WO 96/22997, WO 95/17423 and WO 95/17422 (all assigned to Novo Nordisk A/S); WO 96/15148 (Genentech Inc.); WO 97/22620 (Deghenghi); WO 02/32888, WO 02/32878, WO 00/49037, WO 00/10565 and WO 99/08699 (all assigned to Eli Lilly and Co.); WO 02/057241 and WO 02/056873 (both assigned to Bayer Corp.); and WO 01/85695, WO 00/54729 and WO 00/24398 (all assigned to Bristol-Myers Squibb Co.). The compounds are recommended for use in promoting the growth of food animals, and in humans for treating physiological or medical conditions characterised by a deficiency in growth hormone secretion, and medical conditions which are improved by the anabolic effects of growth hormone. In some of the above-listed disclosures, the list of treatable conditions includes AD.

The compound disclosed in the aforementioned US 5,767,124 has been the subject of a number of clinical trials in therapeutic fields unrelated to AD (see, for example, Murphy et al, *J. Bone Miner. Res.*, **14**,

(1999), 1182-8; Chapman et al, *J. Clinical Endocrinology and Metabolism*, **81**, (1996), 4249-57; *ibid.*, **82**, (1997), 3455-63; and Svensson et al, *ibid.*, **83**, (1998), 362-9).

According to the invention, there is provided a method of treatment or prevention of Alzheimer's disease comprising administering to a subject in need thereof a therapeutically effective amount of a growth hormone secretagogue (GHS) in combination with a therapeutically effective amount of at least one agent which modifies the production or processing of Aβ in the brain, said at least one agent being selected from:

(a) compounds which inhibit the secretion of Aβ;

(b) compounds which selectively inhibit the secretion of the 1-42 isoform of Aβ;

(c) compounds which inhibit the aggregation of Aβ ; and

(d) antibodies which selectively bind to Aβ.

The invention further provides a method of treating, preventing or delaying the onset of dementia associated with Alzheimer's disease, cerebral amyloid angiopathy, multi-infarct dementia, dementia puglistica or Down syndrome comprising administering to a patient in need thereof a therapeutically effective amount of a growth hormone secretagogue in combination with a therapeutically effective amount of at least one agent as defined above which modifies the production or processing of Aβ in the brain.

As used herein, the expression "in combination with" requires that therapeutically effective amounts of both a GHS and an agent which modifies the production or processing of Aβ in the brain (hereinafter termed an "amyloid modifier") are administered to the subject, but places no restriction on the manner in which this is achieved. Thus, the two species may be combined in a single dosage form for simultaneous administration to the subject, or may be provided in separate dosage forms for simultaneous or sequential administration to the subject. Sequential administration may be close in time or remote in time, e.g. one species

administered in the morning and the other in the evening. The separate species may be administered at the same frequency or at different frequencies, e.g. one species once a day and the other two or more times a day. The separate species may be administered by the same route or by different routes, e.g. one species orally and the other parenterally, although oral administration of both species is preferred, where possible. When the amyloid modifier is an antibody, it will typically be administered parenterally and separately from the GHS.

According to a further aspect of the invention there is provided a pharmaceutical composition comprising, in a pharmaceutically acceptable carrier, a growth hormone secretagogue and an amyloid modifier selected from:

(a) compounds which inhibit the secretion of Aβ;

(b) compounds which selectively inhibit the secretion of the 1-42 isoform of Aβ; and

(c) compounds which inhibit the aggregation of Aβ.

The invention further provides the use, for the manufacture of a medicament for treatment or prevention of AD, of a growth hormone secretagogue and an amyloid modifier selected from:

(a) compounds which inhibit the secretion of Aβ;

(b) compounds which selectively inhibit the secretion of the 1-42 isoform of Aβ;

(c) compounds which inhibit the aggregation of Aβ.

The GHS and amyloid modifier act synergistically in reducing the accumulation of Aβ in the brain. Therefore, in a further aspect the invention provides a method for retarding, arresting or preventing the accumulation of Aβ in the brain comprising administering to a subject in need thereof a therapeutically effective amount of a growth hormone secretagogue in combination with a therapeutically effective amount of an amyloid modifier as defined above.

Because of the aforementioned synergistic interaction, it is possible to obtain a beneficial therapeutic effect from the administration of doses of the compounds in question that are smaller than would typically be employed for individual administration of the same compounds. For example, a compound which inhibits secretion of Aβ (such as a γ-secretase inhibitor) may be dosed at a level which does not completely suppress the production of Aβ, yet still exert a therapeutic effect comparable to full suppression thereof, as a result of co-administration of the GHS. This has the potential to prevent side-effects that might arise from the suppression of other activities, unconnected with Aβ production, such as the notch signalling process.

Clearance of Aβ from the brain following administration of the relevant compounds may be evidenced by an increase in the level of soluble Aβ in the cerebrospinal fluid and/or the plasma. Alternatively (or additionally), imaging techniques such as magnetic resonance imaging, positron emission tomography, single photon emission computed tomography and multiphoton microscopy may be employed to monitor the extent of Aβ deposition in the brain (see, for example, Bacskai *et al.*, *J. Cereb. Blood Flow Metab.*, **22** (2002), 1035-41).

In one embodiment of the invention, the GHS and amyloid modifier are administered to a patient suffering from AD, cerebral amyloid angiopathy, multi-infarct dementia, dementia pugilistica or Down syndrome, preferably AD.

In an alternative embodiment of the invention, the GHS and amyloid modifier are administered to a patient suffering from mild cognitive impairment or age-related cognitive decline. A favourable outcome of such treatment is prevention or delay of the onset of AD. Age-related cognitive decline and mild cognitive impairment (MCI) are conditions in which a memory deficit is present, but other diagnostic criteria for dementia are absent (Santacruz and Swagerty, *American Family Physician*, **63** (2001), 703-13). (See also "The ICD-10 Classification

of Mental and Behavioural Disorders", Geneva: World Health Organisation, 1992, 64-5). As used herein, "age-related cognitive decline" implies a decline of at least six months' duration in at least one of: memory and learning; attention and concentration; thinking; language; and visuospatial functioning and a score of more than one standard deviation below the norm on standardized neuropsychologic testing such as the MMSE. In particular, there may be a progressive decline in memory. In the more severe condition MCI, the degree of memory impairment is outside the range considered normal for the age of the patient but AD is not present. The differential diagnosis of MCI and mild AD is described by Petersen *et al.*, *Arch. Neurol.*, **56** (1999), 303-8.

Within this embodiment, the GHS and amyloid modifier are advantageously administered to patients who suffer impaired memory function but do not exhibit symptoms of dementia. Such impairment of memory function typically is not attributable to systemic or cerebral disease, such as stroke or metabolic disorders caused by pituitary dysfunction. Such patients may be in particular people aged 55 or over, especially people aged 60 or over, and preferably people aged 65 or over. Such patients may have normal patterns and levels of growth hormone secretion for their age. However, such patients may possess one or more additional risk factors for developing Alzheimer's disease. Such factors include a family history of the disease; a genetic predisposition to the disease; elevated serum cholesterol; and adult-onset diabetes mellitus.

In a particular embodiment of the invention, GHS and amyloid modifier are administered to a patient suffering from age-related cognitive decline or MCI who additionally possesses one or more risk factors for developing AD selected from: a family history of the disease; a genetic predisposition to the disease; elevated serum cholesterol; and adult-onset diabetes mellitus.

A genetic predisposition (especially towards early onset AD) can arise from point mutations in one or more of a number of genes, including

the APP, presenilin-1 and presenilin-2 genes. Also, subjects who are homozygous for the ε4 isoform of the apolipoprotein E gene are at greater risk of developing AD.

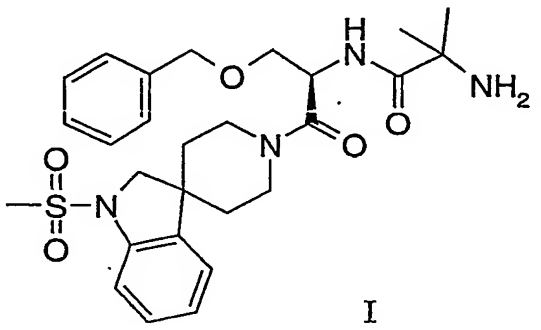
The patient's degree of cognitive decline or impairment is advantageously assessed at regular intervals before, during and/or after a course of treatment in accordance with the invention, so that changes therein may be detected, e.g. the slowing or halting of cognitive decline. A variety of neuropsychological tests are known in the art for this purpose, such as the Mini-Mental State Examination (MMSE) with norms adjusted for age and education (Folstein *et al.*, *J. Psych. Res.*, **12** (1975), 196-198, Anthony *et al.*, *Psychological Med.*, **12** (1982), 397-408; Cockrell *et al.*, *Psychopharmacology*, **24** (1988), 689-692; Crum *et al.*, *J. Am. Med. Assoc'n.* **18** (1993), 2386-2391). The MMSE is a brief, quantitative measure of cognitive status in adults. It can be used to screen for cognitive decline or impairment, to estimate the severity of cognitive decline or impairment at a given point in time, to follow the course of cognitive changes in an individual over time, and to document an individual's response to treatment. Another suitable test is the Alzheimer Disease Assessment Scale (ADAS), in particular the cognitive element thereof (ADAS-cog) (See Rosen *et al.*, *Am. J. Psychiatry*, **141** (1984), 1356-64).

The invention further provides a kit comprising a first medicament comprising a GHS and a second medicament comprising an amyloid modifier together with instructions for administering said medicaments sequentially or simultaneously to a patient suffering from AD, age-related cognitive decline, MCI, cerebral amyloid angiopathy, multi-infarct dementia, dementia pugilistica or Down syndrome.

The GHS used in the invention may be any compound which has the property of stimulating or enhancing secretion of endogenous growth hormone when administered to a subject, for example any of the compounds disclosed in the patents and patent applications listed above.

However, preference is given to compounds which are suitable for oral administration.

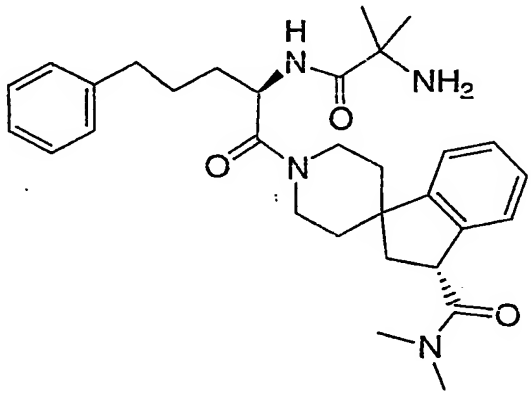
A first class of GHSs suitable for use in the invention is that disclosed in WO 94/13696, in particular the subset thereof disclosed in EP 0615977B, the disclosure of which is incorporated herein by reference. Preferred examples of GHSs within this class include the compound of formula I:



I

named as N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide, and pharmaceutically acceptable salts thereof, in particular the methanesulfonate salt thereof, which may be prepared as described in US 5,767,124.

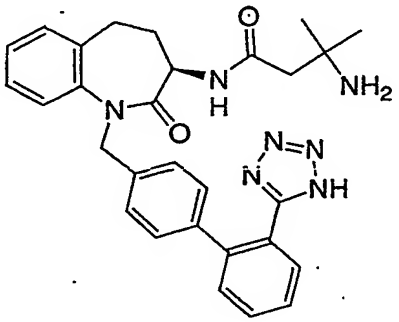
A second class of GHSs suitable for use in the invention is that disclosed in US 5,578,593, the disclosure of which is incorporated herein by reference. Preferred example of GHSs within this class include the compound of formula II:



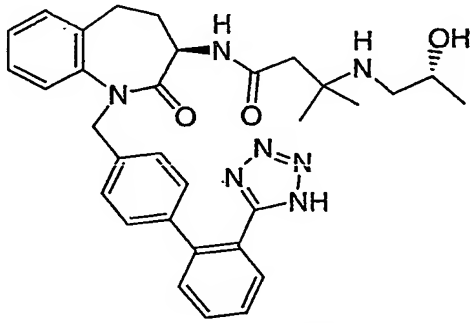
II

and pharmaceutically acceptable salts thereof, which may be prepared as described in US 5,578,593.

A third class of GHSs suitable for use in the invention is that disclosed in WO 92/16524, the disclosure of which is incorporated herein by reference. Preferred example of GHSs within this class include the compounds of formulae III and IV:



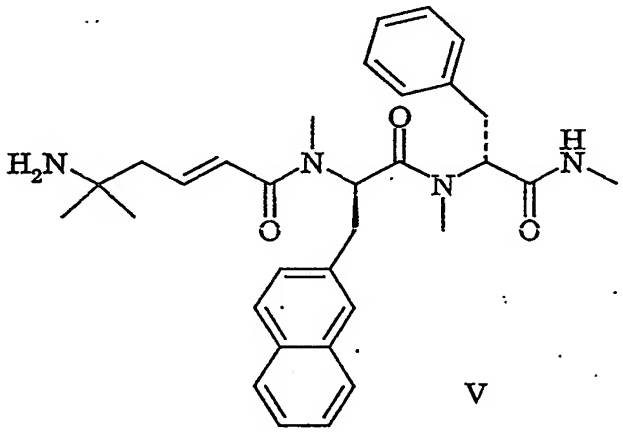
III



IV

and pharmaceutically acceptable salts thereof, in particular the trifluoroacetate salts thereof, which may be prepared as described in WO 92/16524.

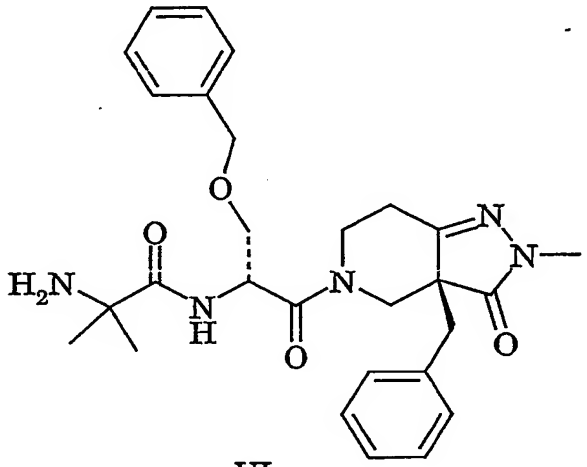
A fourth class of GHSs suitable for use in the invention is that disclosed in WO 97/23508, the disclosure of which is incorporated herein by reference. Preferred examples of GHSs within this class include the compound of formula V, also known as NN703:



V

and pharmaceutically acceptable salts thereof, which may be prepared as described in WO 99/64456.

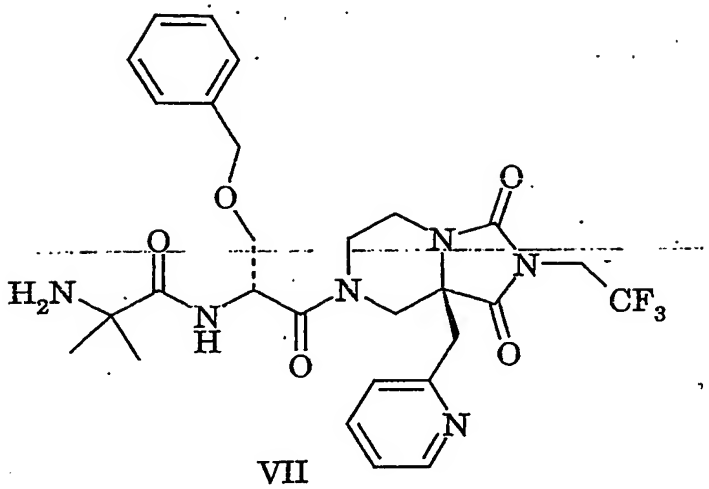
A fifth class of GHSs suitable for use in the invention is that disclosed in WO 97/24369, the disclosure of which is incorporated herein by reference. Preferred examples of GHSs within this class include the compound of formula VI:



VI

named as 2-amino-*N*-[2-(3a-(*R*)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(*R*)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide, and pharmaceutically acceptable salts thereof, in particular the L-tartrate salt, also known as capromorelin, which may be prepared as described in WO 97/24369 and in Carpino et al, *Bioorg. Med. Chem.*, **11** (2003), 581-90.

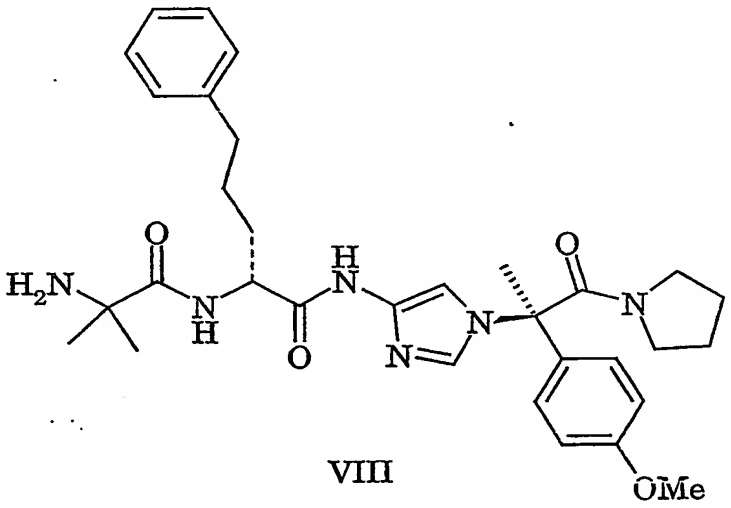
A sixth class of GHSs suitable for use in the invention is that disclosed in WO 98/58947, the disclosure of which is incorporated herein by reference. Preferred examples of GHSs within this class include the compound of formula VII:



VII

and pharmaceutically acceptable salts thereof, which may be prepared as described in WO 98/58947.

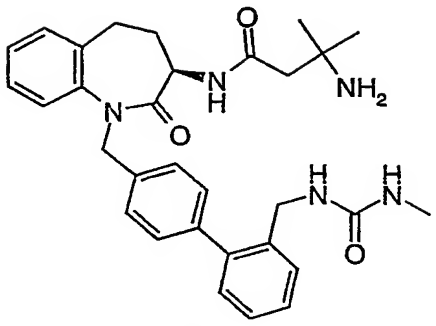
A seventh class of GHSs suitable for use in the invention is that disclosed in WO 99/08699, the disclosure of which is incorporated herein by reference. Preferred examples of GHSs within this class include the compound of formula VIII:



VIII

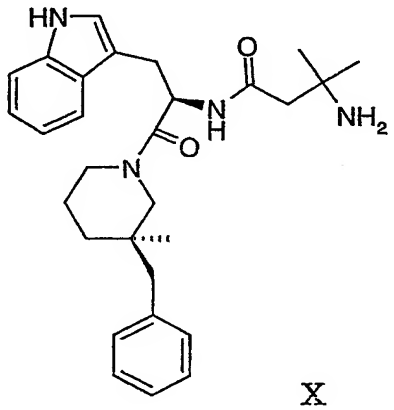
and pharmaceutically acceptable salts thereof, which may be prepared as described in WO 99/08699 and WO 02/32878.

Further GHSs suitable for use in the invention include the compound of formula IX;



IX

and pharmaceutically acceptable salts thereof, which may be prepared as described in De Vita et al, *J.Med.Chem.*, 41 (1998), 1716-28, and the compound of formula X:



X

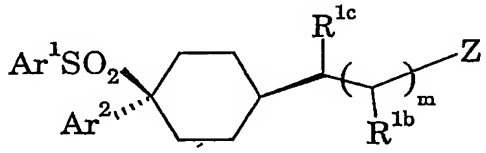
and pharmaceutically acceptable salts thereof, which may be prepared as described in Yang et al, *J.Med.Chem.*, 41 (1998), 2439-41.

Preferably, the GHS is selected from the compounds of formulae I, II, V, VI, VIII and IX depicted above, and their pharmaceutically acceptable salts. Most preferably, the GHS used in the invention is the methanesulfonate salt of the compound of formula I which is in one of the polymorphic forms described in US 5,767,124.

In one embodiment of the invention, the amyloid modifier is a compound which inhibits the secretion of Aβ, for example an inhibitor of of γ-secretase (such as those disclosed in WO 01/53255, WO 01/66564, WO 01/70677, WO 01/90084, WO 01/77144, WO 02/30912, WO 02/36555, WO 02/081435, WO 02/081433, WO 03/018543, WO 03/013506, WO 03/013527 and WO 03/014075), or a β-secretase inhibitor (such as those disclosed in

WO 03/037325, WO 03/030886, WO 03/006013, WO 03/006021, WO 03/006423, WO 03/006453, WO 02/002122, WO 01/70672, WO 02/02505, WO 02/02506, WO 02/02512, WO 02/02520, WO 02/098849 and WO 02/100820), or any other compound which inhibits the formation or release of Aβ, including those disclosed in WO 98/28268, WO 02/47671, WO 99/67221, WO 01/34639, WO 01/34571, WO 00/07995, WO 00/38618, WO 01/92235, WO 01/77086, WO 01/74784, WO 01/74796, WO 01/74783, WO 01/60826, WO 01/19797, WO 01/27108, WO 01/27091, WO 00/50391, WO 02/057252, US 2002/0025955 and US2002/0022621, and also including GSK-3 inhibitors, particularly GSK-3α inhibitors, such as lithium, as disclosed in Phiel et al, *Nature*, **423** (2003), 435-9.

Within this embodiment, the amyloid modifier is advantageously a γ-secretase inhibitor, preferred examples of which include a compound of formula XI:



XI

wherein:

m is 0 or 1;

Z represents halogen, CN, NO_2, N_3, CF_3, OR^{2a}, $N(R^{2a})_2$, CO_2R^{2a}, $OCOR^{2a}$, COR^{2a}, $CON(R^{2a})_2$, $OCON(R^{2a})_2$, $CONR^{2a}(OR^{2a})$, $CON(R^{2a})N(R^{2a})_2$, $CONHC(=NOH)R^{2a}$, heterocyclyl, phenyl or heteroaryl, said heterocyclyl, phenyl or heteroaryl bearing 0-3 substituents selected from halogen, CN, NO_2, CF_3, OR^{2a}, $N(R^{2a})_2$, CO_2R^{2a}, COR^{2a}, $CON(R^{2a})_2$ and C_{1-4}alkyl;

R^{1b} represents H, C_{1-4}alkyl or OH;

R^{1c} represents H or C_{1-4}alkyl;

with the proviso that when m is 1, R^{1b} and R^{1c} do not both represent C_{1-4}alkyl;

Ar^1 represents C_{6-10}aryl or heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CN, NO_2, CF_3, OH,

OCF_3, C_{1-4}alkoxy or C_{1-4}alkyl which optionally bears a substituent selected from halogen, CN, NO_2, CF_3, OH and C_{1-4}alkoxy;

Ar^2 represents C_{6-10}aryl or heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CN, NO_2, CF_3, OH, OCF_3, C_{1-4}alkoxy or C_{1-4}alkyl which optionally bears a substituent selected from halogen, CN, NO_2, CF_3, OH and C_{1-4}alkoxy;

R^{2a} represents H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-6}alkyl, C_{2-6}alkenyl, any of which optionally bears a substituent selected from halogen, CN, NO_2, CF_3, OR^{2b}, CO_2R^{2b}, $N(R^{2b})_2$, $CON(R^{2b})_2$, Ar and COAr; or R^{2a} represents Ar; or two R^{2a} groups together with a nitrogen atom to which they are mutually attached may complete an N-heterocyclyl group bearing 0-4 substituents independently selected from =O, =S, halogen, C_{1-4}alkyl, CN, NO_2, CF_3, OH, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, CO_2H, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, carbamoyl, Ar and COAr;

R^{2b} represents H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-6}alkyl, C_{2-6}alkenyl, any of which optionally bears a substituent selected from halogen, CN, NO_2, CF_3, OH, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, CO_2H, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, carbamoyl, Ar and COAr; or R^{2b} represents Ar; or two R^{2b} groups together with a nitrogen atom to which they are mutually attached may complete an N-heterocyclyl group bearing 0-4 substituents independently selected from =O, =S, halogen, C_{1-4}alkyl, CN, NO_2, CF_3, OH, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, CO_2H, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, carbamoyl, Ar and COAr;

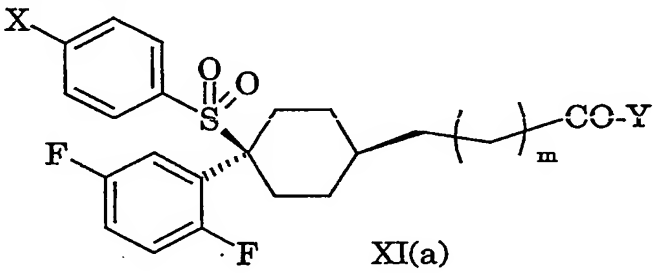
Ar represents phenyl or heteroaryl bearing 0-3 substituents selected from halogen, C_{1-4}alkyl, CN, NO_2, CF_3, OH, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, carbamoyl, C_{1-4}alkylcarbamoyl and di(C_{1-4}alkyl)carbamoyl;

"heterocyclyl" at every occurrence thereof means a cyclic or polycyclic system of up to 10 ring atoms selected from C, N, O and S, wherein none of the constituent rings is aromatic and wherein at least one ring atom is other than C; and

"heteroaryl" at every occurrence thereof means a cyclic or polycyclic system of up to 10 ring atoms selected from C, N, O and S, wherein at least one of the constituent rings is aromatic and wherein at least one ring atom of said aromatic ring is other than C;

... or a pharmaceutically acceptable salt thereof.

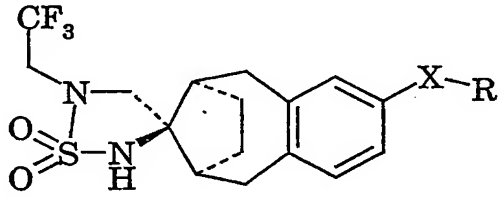
Such compounds may be prepared as described in WO 03/018543. Preferred examples include those defined by formula XIa:



XI(a)

and the pharmaceutically acceptable salts thereof, wherein m is 0 or 1, X is Cl or CF_3, and Y is OH, OC_{1-6}alkyl, NH_2 or NHC_{1-6}alkyl. Particular examples include those in which m is 1 and Y is OH (or the sodium salts thereof), and those in which m is 0 and Y is NH_2 or NHC_{1-6}alkyl.

Another preferred class of γ-secretase inhibitors for use in this embodiment of the invention is that defined by formula XII:



XII

wherein X is a bivalent pyrazole, imidazole, triazole, oxazole, isoxazole, thiazole, isothiazole, thiadiazole or 1,3,4-oxadiazole residue optionally bearing a hydrocarbon substituent comprising 1-5 carbon atoms which is optionally substituted with up to 3 halogen atoms; and

R is selected from:

(i) CF_3 or a non-aromatic hydrocarbon group of up to 10 carbon atoms, optionally substituted with halogen, CF_3, CHF_2, CN, OH, CO_2H, C_{2-6}acyl, C_{1-4}alkoxy or C_{1-4}alkoxycarbonyl;

(ii) a non-aromatic heterocyclic group comprising up to 7 ring atoms of which up to 3 are chosen from N, O and S and the remainder are carbon, bearing 0-3 substituents independently selected from oxo, halogen, CN, C_{1-6}alkyl, OH, CF_3, CHF_2, CH_2F, C_{2-6}acyl, CO_2H, C_{1-4}alkoxy and C_{1-4}alkoxycarbonyl;

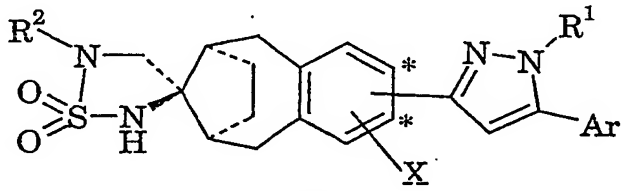
(iii) phenyl or 6-membered heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CF_3, CHF_2, CH_2F, NO_2, CN, OCF_3, C_{1-6}alkyl and C_{1-6}alkoxy; and

(iv) $N(R^a)_2$ where each R^a independently represents H or C_{1-6}alkyl which is optionally substituted with halogen, CF_3, CHF_2, CN, OH, CO_2H, C_{2-6}acyl, C_{1-4}alkoxy or C_{1-4}alkoxycarbonyl;

or a pharmaceutically acceptable salt thereof.

X is very aptly 5-substituted-thiazol-2-yl, 5-substituted-4-methylthiazol-2-yl, 5-substituted-1-methylpyrazol-3-yl, 1-substituted-imidazol-4-yl or 1-substituted-1,2,4-triazol-3-yl. Preferably, R represents optionally-substituted phenyl or heteroaryl such as phenyl, monohalophenyl, dihalophenyl, trihalophenyl, cyanophenyl, methylphenyl, methoxyphenyl, trifluoromethylphenyl, trifluoromethoxyphenyl, pyridyl, monohalopyridyl and trifluoromethylpyridyl, wherein "halo" refers to fluoro or chloro. Particularly preferred identities of R-X- include 5-(4-fluorophenyl)-1-methylpyrazol-3-yl, 5-(4-chlorophenyl)-1-methylpyrazol-3-yl and 1-(4-fluorophenyl)imidazol-4-yl. Such compounds may be prepared by methods similar to those disclosed in WO 02/36555.

Another preferred class of γ-secretase inhibitors for use in this embodiment of the invention is that defined by formula XIII:



XIII

wherein the pyrazole group is attached at one of the positions indicated by an asterisk and X is attached at a position adjacent thereto;

X represents H, OH, C_{1-4}alkoxy, Cl or F;

Ar represents phenyl or 6-membered heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CF_3, CHF_2, CH_2F, NO_2, CN, OCF_3, C_{1-6}alkyl and C_{1-6}alkoxy;

R^1 represents a hydrocarbon group of 1-5 carbon atoms which is optionally substituted with up to 3 halogen atoms; and

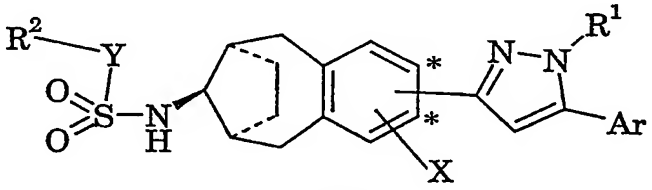
R^2 represents H or a hydrocarbon group of 1-10 carbon atoms which is optionally substituted with up to 3 halogen atoms;

provided that when X is H, R^2 does not represent 2,2,2-trifluoroethyl;

or a pharmaceutically acceptable salt thereof.

Preferred examples of compounds of formula XIII include those in which Ar is 4-fluorophenyl, R^1 is methyl, X is H and R^2 is benzyl, n-propyl, 2,2-dimethylpropyl, n-butyl, isopropyl, t-butyl, 3,3,3-trifluoropropyl, allyl, cyclobutyl or cyclopropylmethyl. Such compounds may be prepared by methods similar to those disclosed in WO 02/36555.

Another preferred class of γ-secretase inhibitors for use in this embodiment of the invention is that defined by formula XIV:



XIV

wherein the pyrazole group is attached at one of the positions indicated by an asterisk and X is attached at a position adjacent thereto;

X represents H, OH, C_{1-4}alkoxy, Cl or F;

Y represents a bond, O or NR^3;

Ar represents phenyl or 6-membered heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CF_3, CHF_2, CH_2F, NO_2, CN, OCF_3, C_{1-6}alkyl and C_{1-6}alkoxy;

R^1 represents a hydrocarbon group of 1-5 carbon atoms which is optionally substituted with up to 3 halogen atoms; and

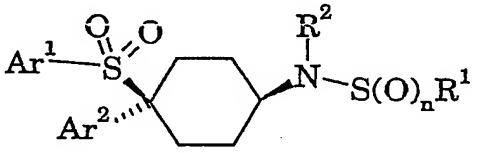
R^2 represents a hydrocarbon group of 1-10 carbon atoms which is optionally substituted with up to 3 halogen atoms, or heteroaryl of 5 or 6 ring atoms optionally bearing up to 3 substituents independently selected from halogen, CF_3, CHF_2, CH_2F, NO_2, CN, OCF_3, C_{1-6}alkyl and C_{1-6}alkoxy; or when Y represents NR^3, R^2 and R^3 together may complete a heterocyclic ring of up to 6 members which optionally bears up to 3 substituents independently selected from halogen, CF_3, CHF_2, CH_2F, NO_2, CN, OCF_3, C_{1-6}alkyl and C_{1-6}alkoxy;

R^3 represents H or C_{1-4}alkyl, or together with R^2 completes a heterocyclic ring as defined above;

or a pharmaceutically acceptable salt thereof.

Preferred examples of compounds of formula XIV include those in which Ar is 4-fluorophenyl, R^1 is methyl, X is H, and either Y is a bond and R^2 is n-butyl, 4-fluorophenyl, 5-chloro-2-thienyl, 5-isothiazolyl, 6-chloropyridin-3-yl or 2-thienyl, or Y is NR^3 and NR^2R^3 is cyclobutylamino, 2,2,2-trifluoroethylamino, n-propylamino, N-methyl-n-propylamino, dimethylamino, pyrrolidin-1-yl or 4-(trifluoromethyl)piperidin-1-yl.

Another preferred class of γ-secretase inhibitors for use in this embodiment of the invention is that defined by formula XV:



XV

wherein n is 1 or 2;

R^1 represents CF_3 or C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-9}cycloalkyl or C_{3-6}cycloalkylC_{1-6}alkyl, any of which may bear up to 2 substituents

selected from halogen, CN, CF_3, OR^3, COR^3, CO_2R^3, $OCOR^4$, SO_2R^4, $N(R^5)_2$, and $CON(R^5)_2$,

or R^1 represents aryl, arylC_{1-6}alkyl, C-heterocyclyl or C-heterocyclylC_{1-6}alkyl;

R^2 represents H or C_{1-4}alkyl;

R^3 represents H, C_{1-4}alkyl, phenyl or heteroaryl;

R^4 represents C_{1-4}alkyl, phenyl or heteroaryl;

R^5 represents H or C_{1-4}alkyl, or two R^5 groups together with a nitrogen atom to which they are mutually attached complete an azetidine, pyrrolidine, piperidine, morpholine, thiomorpholine or thiomorpholine-1,1-dioxide ring;

Ar^1 and Ar^2 independently represent phenyl or heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CN, NO_2, CF_3, CHF_2, OH, OCF_3, CHO, CH=NOH, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, C_{2-6}acyl, C_{2-6}alkenyl and C_{1-4}alkyl which optionally bears a substituent selected from halogen, CN, NO_2, CF_3, OH and C_{1-4}alkoxy;

"aryl" at every occurrence thereof refers to phenyl or heteroaryl which optionally bear up to 3 substituents selected from halogen, CN, NO_2, CF_3, OCF_3, OR^3, COR^3, CO_2R^3, $OCOR^4$, $N(R^5)_2$, $CON(R^5)_2$ and optionally-substituted C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl or C_{2-6}alkenyloxy wherein the substituent is selected from halogen, CN, CF_3, phenyl, OR^3, CO_2R^3, $OCOR^4$, $N(R^5)_2$ and $CON(R^5)_2$; and

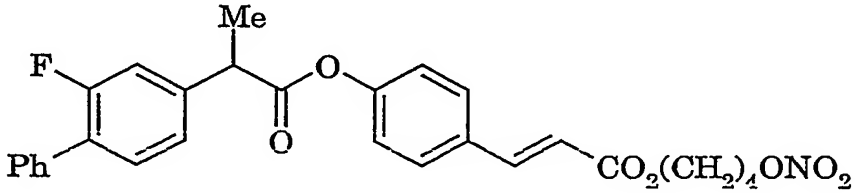
"C-heterocyclyl" and "N-heterocyclyl" at every occurrence thereof refer respectively to a heterocyclic ring system bonded through carbon or nitrogen, said ring system being non-aromatic and comprising up to 10 atoms, at least one of which is O, N or S, and optionally bearing up to 3 substituents selected from oxo, halogen, CN, NO_2, CF_3, OCF_3, OR^3, COR^3, CO_2R^3, $OCOR^4$, OSO_2R^4, $N(R^5)_2$, $CON(R^5)_2$ and optionally-substituted phenyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl or C_{2-6}alkenyloxy wherein the

substituent is selected from halogen, CN, CF_3, OR^3, CO_2R^3, $OCOR^4$, $N(R^5)_2$ and $CON(R^5)_2$;

or a pharmaceutically acceptable salt thereof.

Preferred examples of compounds of formula XV include those in which R^1 is CF_3, Ar^2 is 2,5-difluorophenyl and Ar^1 is 4-chlorophenyl, 4-trifluoromethylphenyl or 6-trifluoromethylpyridin-3-yl. Compounds of formula XV may be prepared by reaction of R^1SO_2Cl with the appropriate 4-aryl-4-arylsulphonylcyclohexylamine, the synthesis of said cyclohexylamines being described in WO 02/081435.

In a second embodiment of the invention, the amyloid modifier is a compound which selectively inhibits secretion of the 1-42 isoform of Aβ. Suitable examples of such compounds include the non-steroidal antiinflammatory drugs (NSAIDs) and their analogues disclosed in WO 01/78721 and US 2002/0128319, such as sulindac sulfide, flufenamic acid, ibuprofen, flurbiprofen, fenoprofen, mefenamic acid, indomethacin and (R)-flurbiprofen. A preferred example is (R)-flurbiprofen. Alternatively, an NSAID derivative capable of releasing nitric oxide may be employed (e.g. compounds as disclosed in WO 02/092072 and in Jantzen et al, *J. Neuroscience*, **22** (2002), 226-54). Preferred examples of NO-releasing compounds include the 4-nitrooxybutyl ester of flurbiprofen (made by NiCox and also known as HCT-1026) and the compound:



known as NCX-2216 (NiCox). As a further alternative within this embodiment, a compound which modulates the activity of PPARα and/or PPARδ (as disclosed in WO 02/100836) may be employed.

In a third embodiment of the invention, the amyloid modifier is a compound which inhibits the aggregation of Aβ. Suitable examples include chelating agents such as clioquinol (Gouras and Beal, *Neuron*, **30**

(2001), 641-2) and the compounds disclosed in WO 99/16741, in particular that known as DP-109 (Kalendarev et al, *J. Pharm. Biomed. Anal.*, 24 (2001), 967-75). Other inhibitors of Aβ aggregation suitable for use in the invention include the compounds disclosed in WO 96/28471, WO 98/08868 and WO 00/052048, including the compound known as Apan™ (Praecis); WO 00/064420, WO 03/017994, WO 99/59571 and the compound known as Alzhemed™ (Neurochem); WO 00/149281 and the compositions known as PTI-777 and PTI-00703 (ProteoTech); WO 96/39834, WO 01/83425, WO 01/55093, WO 00/76988, WO 00/76987, WO 00/76969, WO 00/76489, WO 97/26919, WO 97/16194, and WO 97/16191.

In a fourth embodiment of the invention, the amyloid modifier is an antibody which binds selectively to Aβ. Said antibody may be polyclonal or monoclonal, but is preferably monoclonal, and is preferably human or humanized. Preferably, the antibody is capable of sequestering soluble Aβ from biological fluids, as described in WO 03/016466, WO 03/016467, WO 03/015691 and WO 01/62801. Suitable antibodies include humanized antibody 266 (described in WO 01/62801) and the modified version thereof described in WO 03/016466.

In a particular embodiment of the invention, the amyloid modifier is selected from:

(a) compounds which inhibit the secretion of Aβ;

(b) compounds which selectively inhibit the secretion of the 1-42 isoform of Aβ;

(c) compounds which inhibit the aggregation of Aβ.

Depending on whether they are to be administered together or separately, the GHS and amyloid modifier are typically supplied as single or multiple pharmaceutical compositions comprising the active species and a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, transdermal patches, auto-injector devices or

suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. The principal active ingredient typically is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate and dicalcium phosphate, or gums, dispersing agents, suspending agents or surfactants such as sorbitan monooleate and poly(ethylene glycol), and other pharmaceutical diluents, e.g. water, to form a homogeneous preformulation composition containing one or both active species, or pharmaceutically acceptable salts thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active species is or are dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This preformulation composition is then subdivided into unit dosage forms of the type described above, generally containing from 0.01 to about 500 mg of the active species. Typical unit dosage forms contain from 0.05 to 100 mg, for example 0.05, 0.1, 0.5, 1, 2, 5, 10, 25, 50 or 100 mg, of the active species. Tablets or pills of the pharmaceutical composition(s) can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the pharmaceutical compositions useful in the present invention may be incorporated for administration orally or by injection include aqueous solutions, liquid- or gel-filled capsules,

suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, poly(ethylene glycol), poly(vinylpyrrolidone) and gelatin.

Pharmaceutical compositions suitable for oral administration are preferred, except when the amyloid modifier is an antibody, in which case parenteral administration of the antibody is preferred, e.g. by subcutaneous, intravenous or intraperitoneal injection.

For treatment or prevention of AD, the GHS and amyloid modifier may be dosed at the levels which are effective for the original purposes of the separate compounds. Thus, the GHS will typically be dosed at levels known to provide increased secretion of endogenous growth hormone in a human subject, and the amyloid modifier at levels known to cause significant inhibition of the secretion of Aβ, or of the 1-42 isoform thereof, or significant inhibition of the aggregation of Aβ, or significant sequestration of soluble Aβ, as appropriate. In many cases, these dosage levels are available from the published literature, but otherwise are readily determined by standard clinical methods. However, as explained above, it may be possible and advantageous to use a smaller dose of the amyloid modifier than would otherwise be indicated, in view of the synergistic interaction with the GHS.

The frequency of dosing of the relevant compounds (e.g. once, twice, three times or four times per day) may be selected according to the pharmacokinetic profiles of the compounds concerned.

In the case of the preferred GHS of formula I, doses of about 0.01 to 5.0 mg/kg per day, preferably about 0.05 to 2.5 mg/kg per day, more preferably about 0.1 to 1.0 mg/kg of body weight per day, may be

contemplated. In particular, a dose equivalent to 5mg, 10 mg or 25 mg of the free base may be administered orally once daily to a patient.

In the case of a compound which inhibits the secretion of Aβ, the dosage may be adjusted so as to provide complete suppression of the secretion of Aβ, or only partial suppression thereof, for example a 50% reduction in Aβ secretion. In the case of a γ-secretase inhibitor of formula XI or XII above, daily oral doses of about 25 to 500mg per person are contemplated, in particular about 50 to 250mg per person.

In a further aspect, the invention provides a pharmaceutical composition comprising, in a pharmaceutically acceptable carrier, a compound of formula I or a pharmaceutically acceptable salt thereof and a compound of formula XI(a) or a pharmaceutically acceptable salt thereof. Preferably the compound of formula I is in the form of the methanesulfonate salt. Preferably, the pharmaceutical composition is in a unit dose form suitable for oral administration, such as a tablet or a capsule. In a particular embodiment, said unit dose form contains the equivalent of 5, 10 or 25 mg of the free base of formula I and the equivalent of from 50 to 250 mg of the compound of formula XI(a).